Individual Differences in the Kinetics of Alcohol Absorption and Elimination

A Human Study

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Accepted for publication:
December 10, 2004

Abstract

The individual differences in alcohol pharmacokinetics were studied using the one-compartment model with first-order absorption and zero-order elimination kinetics in humans. The blood alcohol concentrations (BACs) were simulated by obtained parameters, absorption rate constant (ka), and elimination rate constant (β). The 81 healthy young Japanese volunteers, who had been divided into those without alcohol-induced facial flushing (nonflushers) and those with facial flushing (flushers) according to alcohol patch test results and a questionnaire beforehand, ingested 0.50 g/kg ethanol within 1 minute. Breath alcohol concentrations (BrACs) were measured during absorption and during the elimination period. BACs were obtained based on BrACs. Fifteen percent of subjects exhibited low BAC profile (below 0.4 mg/mL) (first-pass effect [FPE] group), although the majority showed normal BAC profile (normal group). The ka was approximately 5 to 8 (h−1) in the normal group without significant difference between nonflushers and flushers, whereas that in the FPE group was significantly smaller than in the normal group. For the normal group, peak BACs were well simulated by the one-compartment model with first-order absorption and zero-order elimination kinetics. A considerable portion of subjects exhibited FPE. Absorption of alcohol from the intestine plays an important role in alcohol pharmacokinetics in humans.

Key Words: Alcohol pharmacokinetics; absorption rate constant; first-pass effect; human study.


Alcohol pharmacokinetics are generally analyzed using the one-compartment model with zero-order elimination kinetics (1), which is applicable to relatively high blood alcohol concentrations (BAC). However, this model ignores the kinetics of absorption and distribution of alcohol. Alcohol pharmacokinetics generally follows the one-compartment model when alcohol is administered orally. We previously reported absorption rate constant (ka) value in a rabbit model by using the one-compartment model with first-order absorption and zero-order elimination kinetics (2). However, the ka for alcohol has not been studied in Japan. About 40% of the Japanese population shows aldehyde dehydrogenase 2 deficiency with facial flushing (flushers) owing to high blood levels of acetaldehyde (3). It has been reported that the accumulation of acetaldehyde inhibits the absorption of alcohol in rat intestine (4). However, the relationship between the flushing phenomenon and absorption kinetics has not been shown.

In this study, we analyzed alcohol pharmacokinetics using the one-compartment model with first-order absorption and zero-order elimination kinetics in healthy volunteers after a single ingestion of alcohol. We calculated the ka value and compared the pharmacokinetics in flushers with that in nonflushers.

MATERIALS AND METHODS

Healthy Japanese subjects (N = 81) ranging from 21 to 27 years of age were used under informed consent. The
For the purpose of = 3); the value was used on an IBM-compatible microcomputer values were estimated using the n = 51). The BAC in the FPE group remains below 0.4 mg/mL = 29). We (mg .mL–1 .h–1) = zero-order elimination phy period and measured BAC by head-space gas chromatogra- the instrument with a mouthpiece tube (6). Through simultaneous measurements of BAC and BrAC, the ratios of BAC to BrAC were calculated (2401 ± 517 [mean ± SD]; Pearson's correlation coefficient: r = 0.767, n = 29). We used Fisher's Z-transformation for approximation to the normal distribution [Z = (1/2)ln(1 + r)/(1 – r) = 1.013, Z0 = Z(n – 3)1/2 = 5.165 > z(0.0001/2) = 3.891; p < 0.0001]. The value of the ratio we obtained is slightly higher than usually reported (2100); the coefficient between the two assays was not so strong. In this experiment, we adopted the ratio (2401) because we obtained the value in the same experimental conditions. We estimated the BAC from noninvasive BrAC. The first-pass effect (FPE) group was defined as those subjects who showed neither clear peaks of BACs nor maximum BAC below 0.4 mg/mL; the other majority (normal group) showed clear peaks of BAC as shown in Fig. 1. For the normal group, we conducted the following kinetic study. We used a one-compartment model with first-order absorption and zero-order elimination kinetics. The equation used was:

\[ C = D/(Vd/F)[1 - \exp(-ka .t)] - \beta \]  

(Eq. 1)

where: C (mg · mL⁻¹) = BAC; D (g · kg⁻¹) = dose (0.50); ka (h⁻¹) = absorption rate constant; Vd/F (l · kg⁻¹) = distribution volume/ bioavailability; \( \beta \) (mg · mL⁻¹ · h⁻¹) = zero-order elimination rate constant.

These parameters were estimated using the weighted non-linear least-squares method. The estimated initial value was determined via linear regression analysis. The modified Marquardt method was used for curve-fitting as shown previously (7). In these kinetic studies, the computer program MULTI (8) was used on an IBM-compatible microcomputer (FMV Deskpower, Fujitsu, Tokyo, Japan). The numbers of the normal group and the FPE group, or nonflushers and flushers, are shown in Table 1. For kinetic study, nonflushers and flushers in the normal group were analyzed separately. The data of the cases, which are not curve-fitted, were omitted. For the FPE group, \( \text{ka} \) and \( \beta \) values were estimated using the first-order absorption model and the regression curve, respectively. Data are expressed as the mean ± SD and were analyzed using Student’s unpaired t-test.

RESULTS

Sixty-three percent (51/81) of the subjects followed the first-order absorption and zero-order elimination kinetic model (normal group); 22% (18/81) did not, whereas 15% (12/81) showed FPE with a low ka of 2.21 ± 0.76 (FPE group, including both nonflushers and flushers) compared with a ka of 6.65 ± 5.11 in the normal group, including both nonflushers and flushers (Fig. 2A). These FPE group subjects showed lower BACs with their peaks below 0.4 mg/mL (Fig. 1) and were excluded for the curve-fitting studies.

For nonflushers, the mean ka value (Fig. 2A) and the \( \beta \) value (Fig. 2B) in the FPE group was significantly smaller than those in the normal group. To examine the effect of acetaldehyde on the alcohol disposition profile, we then compared the ka and

![Fig. 1. Blood alcohol concentration (BAC) in the first-pass effect (FPE) group and the normal group with curve-fitting.](image-url)

**Table 1**

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<th>Total number</th>
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<th>Curve fitted or not</th>
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<th>Flusher</th>
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**Grouping of Subjects Used in the Present Study**

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<td>FPE group</td>
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